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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/014,812	12/14/2001	Stephen Palmer	05569.0012.cpus12	1664

22930 7590 12/23/2004

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EXAMINER	
LIU, SAMUEL W	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 12/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/014,812	PALMER ET AL.	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3 and 5-30* is/are pending in the application.

4a) Of the above claim(s) *7-27,29 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,5,6 and 28* is/are rejected.

7)☒ Claim(s) *3* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10-21-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

Claims 2-3 and 5-30 are pending.

The applicants' amendment filed 21 October 2004, which cancels claims 1 and 4, and amends claims 2-3, 5-6 and 28 has been entered. Also, the applicants' request (filed 21 October 2004) for extension of time of two months has been entered. Note that claims 7-27 and 29-30 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention (see the Office action mailed 19 May 2004). Thus, the pending claims 2-3, 5-6 and 28 are examined in this Office action.

Please note that grounds of objection and/or rejection not explicitly restated and/or set forth below are withdrawn.

IDS

The reference of IDS filed 21 October 2004 have been considered.

Claim Objection

The disclosure is objected to because of the following informalities:

In claim 3 "PDE4" should be changed to "phosphodiesterase 4 isoform (PDE4)".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-3, 5-6 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not describe (i) all phosphodiesterase (PDE) inhibitors have ability of inducing ovulation (note that claim1 recites "*a phosphodiesterase*" which encompasses all subtypes of PDE molecules (see below)); the specification describes and provides working examples for PDE subtype 4 (i.e., PDE4) inhibitors (e.g., compounds 1-4 in Examples 1-8) have said ability; and (ii) modulator which includes inhibitor and stimulator, of cAMP level for inducting ovulation.

Thus, applicants are not in possession of a method of inducing ovulation comprising administering to a subject a non-polypeptide cAMP level modulator which is any PDE inhibitor having activity of hydrolyzing cAMP.

There are 11 PDE subtypes; of them, PDE 4 and PDE 7 are cAMP specific (i.e., specifically hydrolyzes cAMP phosphodiester bond). As yet, there is no art teaching that, like the pDE4, the PDE7 enzyme has ability of inducing ovulation or enhancing gonadotropin (e.g., hCG)-mediated ovulation. Applicants need to provide written description for PDE inhibitors that hydrolyze cAMP, e.g., PDE7, in order for enablement for the claimed method.

Moreover, Conti et al. (US Pat. No. 6110471) have shown that the PDE3-specific inhibitor prevents oocytes maturation thereby inhibits ovulation (see the patent claims 1-3 and 14 and columns 3-4), i.e., the PDE3 specific inhibitor has the opposite role in ovulation compared to

PDE4 specific inhibitor. This indicates that not all PDE inhibitors have ability of inducing ovulation. Thus, without written description, one cannot know a compound inhibiting a PDE (e.g., PDE3) can elevate a cAMP level; thereby promote ovulation induction. Therefore, applicants are not in possession of the method of inducing ovulation comprising administering to a subject an inhibitor of PDE hydrolyzing cAMP that encompasses any inhibitors of the said PDE subtypes.

The applicants' response to the rejection under 35 USC 112, the first paragraph

In page 8-10, the response filed 21 October 2004 asserts that the Examiner has mischaracterized the scope of the claimed invention by failing to take into account the entire specification (page 8, the 2nd paragraph) as the claimed non-polypeptide cAMP level inhibitor encompasses any compounds that have activity of increasing intracellular level of cAMP (see the paragraphs on the bridging pages 7-8), e.g., the PDE inhibitor (genus) including all the PDE inhibitors which degrade cAMP (see page 9, the last paragraph to page 10, the 1st paragraph). The applicants' argument has been considered but it is found to be not persuasive because (i) the instant application neither describes nor teaches non-phosphodiesterase inhibitors which enhance cAMP level and thus induce ovulation, (ii) the instant disclosure does not describe inhibitor of PDE7, or/and PDE8, or/and PDE10, or/and PDE11, which hydrolyze cAMP, have ability of inducing the ovulation thereof. Thus, the applicants are not in possession of said method using (*a*) any organic compounds which is the non-polypeptide cAMP level modulator and (*b*) except PDE4, any inhibitors of PDE that are the non-polypeptide cAMP level enhancer and have ability of inducing/inducing ovulation. Therefore, the rejection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 2-3, 5-6 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 sets forth the broader limitation "non-polypeptide cAMP level modulator" and also recites "... modulator is *a* phosphodiesterase inhibitor" (i.e., a cAMP level stimulator) which is the narrower statement of the limitation. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Also, claim 2 is awkward and not apparent in "a phosphodiesterase inhibitor of a phosphodiesterase" does "a phosphodiesterase" (follows "inhibitor") refer to the phosphodiesterase (before "inhibitor") thereof? Suggest "an inhibitor of phosphodiesterase". See also claim 5. Further, claim 2 there appears to be insufficient antecedent basis for this limitation "said cAMP level modulator" in the claim (note that "*non-polypeptide cAMP level modulator*" in the specification has been defined as in an entity (see page 14, [0039]) but not "*cAMP level modulator*"). The dependent claims are also rejected.

Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2-3, 5-6 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martins, T. J. et al. (US Pat. No. 6423710) and further in view of Garvey, D. S. et al. (US Pat No. 5958926).

In the table depicted on columns 2000-202, Martins et al. teach 94 non-polypeptide PDE4 inhibitors.

At column 21, lines 3-6, Martins et al. teach that the said PDE4 inhibitors elevate cAMP levels within granulose cells, and thereby promote gonadotropin induction of ovulation, as applied applied to the instant claim 2-3 and 5-6.

At column 203, lines 23-26, Martin et al. teach it is well known that PDE4 inhibitors (e.g., rolipram) increases cAMP levels. At columns 19 and 21, Martin et al. teach a method of modulating cAMP level in a mammal.

Martins et al. do not expressly teach that the PDE4 inhibitor is *Piclamilast* (see column 9, lines 11-14). Note that applicants have elected *Piclamilast* for examination (see the applicants'

response to the restriction requirement filed 19 March 2004). Garvey et al. teach *Piclamilast* is a PDE4 inhibitor, as applied to the instant claim 28.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to induce ovulation by administering to a female in need the PDE4 inhibitor, e.g., *Piclamilast*, as taught by Garvey et al., because Martins et al. have taught that PDE4 inhibitors are routinely used to increasing cAMP levels and has ability of enhancing oocyte maturation and ovulation (see the above statement) wherein said inhibitors induce ovulation through a mechanism of *enhancing gonadotropin induction of ovulation*; additionally, there is an advantage of using the PDE4 inhibitor as useful in the treatment of s disease state, e.g., inflammation as taught by Martins et al. (see column 18, lines 36-38) (note that inflammation is often associated with process of ovulation); and because the Garvey's PDE inhibitor compound has been formulated in a pharmaceutical composition administrable to female, as taught by Garvey et al. (see the patent claims 16-17). Thus, the skilled artisan would have employed the said PDE inhibitor to induce/enhance ovulation in a female with successful expectation. Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

The applicants' response to the rejection under 35 USC 103

The response filed 21 October 2004 argues that the citation from the Martins' patent teaching relies on Tsafriri' s reference (cited in the Office action mailed 19 may 2004), and that Tsafriri et al. merely propose an untested hypothetical model and Martins et al. mischaracterize the disclosure of the Tsafriri by stating that PDE4 inhibitors can induce ovulation *in vivo*. The response asserts that induction of ovulation by the PDE inhibitor thereof is completely unknown

at the time the application was filed and that the cited references (Martins and Tsafriri) do not disclose with any certainty that elevated cAMP levels would induce ovulation (see page 12, the 3rd paragraph to page 13). The applicants' argument is found to be unpersuasive because, in abstract, Tsafriri et al. have positively provided a motivation for the PDE inhibitor ability of inducing ovulation, i.e., inhibitor of cAMP-specific PDE (PDE4) can enhance action of key hormone for ovulation, i.e., gonadotropin, in ovulation process, and in Table 1 (page 399) Tsafriri et al. have demonstrated that Rolipram, a PDE4 inhibitor, but not milrinone and cilostamide (both are PDE3 inhibitors), stimulates oocyte maturation and hCG (gonadotropin)-mediated ovulation process. Thus, prior to the time when this application was filed, it has been known in the art that the PDE4 inhibitor can be used for enhancing ovulation that is mediated by the ovulatory hormone, gonadotropin, *in vivo*; and the skilled artisan would have readily employed the said PDE inhibitor to induce/enhance ovulation in a female, which would have led to arriving at the current invention. Because, on page 398, Tsafriri et al. have clearly indicated that unlike PDE3 inhibitor, Rolipram - a specific PDE4 inhibitor induces the oocyte maturation that is necessary for ovulation, and because, in Table 1, Tsafriri et al. have evidenced the effect of the Rolipram on stimulating ovulation, it would have been certain to the skilled artisan to choose the PDE4 inhibitor but not the PDE3 inhibitor (*note that the PDE3 inhibitor and PDE4 inhibitor are currently known two agents involving oocyte maturation and/or ovulation process*)) for inducing ovulation. Administration of a PDE4 inhibitor therefore would have resulted in the claimed ovulation induction. Thus, the rejection is maintained.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is571-272-0949. The examiner can normally be reached from 9:00 a.m. to 5:30 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Weber, Jon, can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

Samuel Wei Liu, Ph.D.
Art Unit 1653, Examiner
December 17, 2004

ROBERT A. WAX
PRIMARY EXAMINER
Art Unit 1653